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Strategies for cancer clinical trials with multiple biomarkers

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Planning and analyzing a multiple biomarker trial is a challenging task comprising various factors which have to be considered. It is an area of ongoing research and only a limited number of multiple biomarker trials have already been completed and their results published. Learning from these completed trials is an important part of the planning process, which can help to avoid issues and pitfalls that these trials may have encountered.

Some of the issues which were reported by completed trials, such as low prevalence of the biomarkers and not being able to react to the latest developments regarding biomarkers and treatments, are addressed in this thesis.

Sample size calculation and data analysis methods for testing an overall treatment strategy are investigated for situations where biomarker prevalences make it unfeasible to test within the individual biomarker-groups. Additionally, the issue of a large number of biomarker-negative patients is addressed, which is a side effect in trials that investigate lower prevalence biomarkers. Different analysis approaches for a trial that includes biomarker-negative patients are compared and it is examined whether inclusion of biomarker-negative patients in the analysis can improve bias and standard deviation of the treatment effect estimates. Finally, a flexible study design is considered that allows a new biomarker-group with corresponding experimental treatment to be included in the study after accrual has already begun. Different aspects of study design modification are discussed and different models for analysis of such a study are compared. Furthermore, the issue of missing biomarker data is addressed. If the initial biomarker screening did not include the new biomarker before it was added to the study, the biomarker status regarding this biomarker has to be determined retrospectively for patients that are included in the study before adding the new biomarker. This may lead to missing data for some or all of the patients. For cases where data is only partially missing, different methods for missing data imputation for models with interaction terms are investigated and compared.

The first issue of three issues which are addressed in this thesis is low prevalence of the biomarkers. For a study which tests an overall biomarker-guided treatment strategy, the sample size calculation method by Palta and Amini appears to be the most appropriate choice when heterogeneous treatment effects are expected. The results from the simulation study suggest that the subsequent data analysis could be performed using the two-step approach suggested by Mehrotra or a shared frailty model. If no other covariates are included in the model, an exact log-rank test could also be used. The asymptotic log-rank test and the stratified Cox PH model suffers loss of power in the simulation study and therefore should not

be used for heterogeneous treatment effects. To test the individual biomarker-groups as secondary hypotheses after testing the overall treatment strategy, some strategies for multiple testing are suggested.

The second issue that is addressed is a large expected number of biomarker-negative patients at the screening stage. For a situation where an overall biomarker-guided treatment strategy is not desirable, a combined analysis model using the data from the entire study, including biomarker-negative patients, is investigated. This combined model estimates the treatment effects for the individual biomarkers. Application of the Firth correction appeared to be a good method for reduction of small sample size bias, which is likely to occur for low prevalence biomarkers. The inclusion of biomarker-negative patients in the model can provide a small additional benefit with respect to reduction of bias and standard deviation.

The third issue considered is the constant discovery of new biomarkers and corresponding biomarker-guided experimental therapies. It is desirable for a clinical trial to be able to react to these continuous developments by investigating options to add new biomarkers and corresponding therapies to an ongoing study. Different models for data analysis are compared for a situation with a belatedly added biomarker, an overlap of biomarkers within the population, and an effect of the new biomarker on the response to the experimental treatment of an already existing biomarker-group. Adding an interaction term to the combined analysis model can help avoiding biased treatment effect estimates when there is overlap of the biomarkers within the patient population, and when patients with both biomarkers respond differently to the experimental therapy than patients with only one of the biomarkers. If there is missing data regarding the biomarker status of the belatedly added biomarker, data imputation can be utilized. However, the correct model specification is crucial to avoid biased estimates when interaction terms are part of the model for the final analysis. These interaction terms should already be included in the imputation model rather than imputing them passively. The simulation study suggests that for the considered scenario, the `just-another-variable'-approach with polytomous logistic regression is the best option to avoid obtaining biased estimates after data imputation.

Due to the heterogeneity of biomarkers and treatments and the rapid developments in this field, the planning phase of a multiple-biomarker trial is a complex process and each trial has to be adjusted to the individual situation. This thesis can give guidance in some of the aspects that need to be considered, but of course there are many more aspects that need to be addressed.